



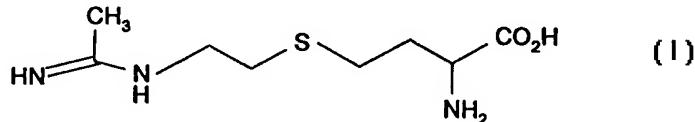
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(54) Title: NITRIC OXIDE SYNTHASE INHIBITORS

(57) Abstract

The present invention relates to novel amidino compounds of formula (I), to a process for their manufacture, to pharmaceutical compositions containing them, and to their use in therapy, in particular their use as selective inhibitors of inducible nitric oxide synthase.



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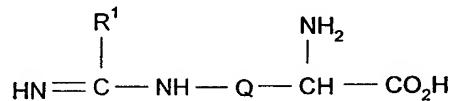
NITRIC OXIDE SYNTHASE INHIBITORS

The present invention relates to novel amidino compounds, to a process for their manufacture, to pharmaceutical compositions containing them, and to their use in therapy, in particular their use as selective inhibitors of inducible nitric oxide synthase.

Nitric oxide is the endogenous stimulator of the soluble guanylate cyclase enzyme and is involved in a number of biological actions. Excess nitric oxide production is also thought to be involved in a number of conditions, including septic shock and many inflammatory diseases. The biochemical synthesis of nitric oxide from L-arginine is catalysed by the enzyme NO synthase. Many inhibitors of NO synthase have been described and proposed for therapeutic use.

More recently, it has been an object in this field to provide NO synthase inhibitors displaying selectivity for either inducible NO synthase (iNOS) or neuronal NO synthase (nNOS) over endothelial NO synthase (eNOS).

Thus WO93/13055 describes selective NO synthase inhibitors of formula



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and salts, and pharmaceutically acceptable esters and amides thereof, in which:

R_1 is a C_{1-6} straight or branched chain alkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, a C_{3-6} cycloalkyl group or a C_{3-6} cycloalkyl C_{1-6} alkyl group;

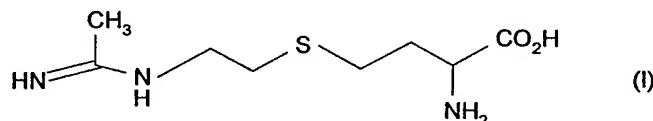
25 Q is an alkylene, alkenylene or alkynylene group having 3 to 6 carbon atoms and which may optionally be substituted by one or more C_{1-3} alkyl groups;

a group of formula $-(\text{CH}_2)_p\text{X}(\text{CH}_2)_q-$ where p is 2 or 3, q is 1 or 2 and X is $\text{S}(\text{O})_x$ where x is 0, 1 or 2, O or NR^2 where R^2 is H or C_{1-6} alkyl; or

30 a group of formula $-(\text{CH}_2)_r\text{A}(\text{CH}_2)_s-$ where r is 0, 1 or 2, s is 0, 1 or 2 and A is a 3 to 6 membered carbocyclic or heterocyclic ring which may optionally be substituted by one or more suitable substituents such as C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, halo, nitro, cyano, trifluoro C_{1-6} alkyl, amino, C_{1-6} alkylamino or di C_{1-6} alkylamino.

We have now found compounds falling within the scope of WO 93/13055 which as well as being selective iNOS inhibitors, display advantages including that they have a long half-life and are orally bioavailable when administered *in vivo*.

5 Therefore, according to the present invention there is provided a compound of formula (I)



10 or a salt, solvate, or physiologically functional derivative thereof.

Formula (I) includes an asymmetric centre in the amino acid group, and although the natural L or (S) configuration of arginine is preferred, it is intended that formula (I) includes both (S) and (R) enantiomers either in substantially pure form or admixed in any proportions.

15 Thus, in the alternative, the present invention provides a compound selected from:

(R/S)-[2-(1-iminoethylamino)ethyl]-DL-homocysteine
 (S)-[2-(1-iminoethylamino)ethyl]-L-homocysteine; and
 (R)-[2-(1-iminoethylamino)ethyl]-D-homocysteine

20 and salts, solvates, and physiologically functional derivatives thereof.

In a preferred aspect, the present invention provides (S)-[2-(1-iminoethylamino)ethyl]-L-homocysteine or a salt, solvate, or physiologically functional derivative thereof. In a particularly preferred aspect, the present invention provides (S)-[2-(1-iminoethylamino)ethyl]-L-homocysteine or a salt thereof.

25 Salts and solvates of compounds of formula (I) which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of formula (I) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives.

By the term "physiologically functional derivative" is meant a chemical derivative of a compound of formula (I) having the same physiological function as the free compound of formula (I), for example, by being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include esters, amides, and carbamates; preferably esters and amides.

Suitable salts according to the invention include those formed with both organic and inorganic acids or bases. Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, succinic, oxalic, fumaric, maleic, oxaloacetic, methanesulphonic, ethanesulphonic, p-toluenesulphonic, benzenesulphonic, and isethionic acids. Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases such as dicyclohexyl amine and N-methyl-D-glucamine.

Pharmaceutically acceptable esters and amides of the compounds of formula (I) may have the acid group converted to a C₁₋₆alkyl, aryl, aryl C₁₋₆ alkyl, or amino acid ester or amide. Pharmaceutically acceptable amides and carbamates of the compounds of formula (I) may have an amino group converted to a C₁₋₆alkyl, aryl, aryl C₁₋₆ alkyl, or amino acid amide or carbamate.

As mentioned above, the compounds of formula (I) are inhibitors of NO synthase as demonstrated in the NOS inhibition assays below.

Therefore, compounds of formula (I) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives have use in the prophylaxis and treatment of clinical conditions for which an inhibitor of NO synthase is indicated, in particular, an inhibitor of iNOS. Such conditions include inflammatory conditions, shock states, immune disorders, and disorders of gastrointestinal motility. The compounds of formula (I) and pharmaceutically acceptable salts, solvates, and physiologically functional derivatives thereof may also be of use in the prophylaxis and treatment of diseases of the central nervous system including migraine.

By shock states is meant those resulting from overproduction of NO, such as septic shock, haemorrhagic shock, traumatic shock, or shock caused by fulminant hepatic failure or by therapy with cytokines such as TNF, IL-1 and IL-2

or therapy with cytokine-inducing agents, for example 5,6-dimethylxanthenone acetic acid.

Examples of inflammatory conditions and immune disorders include those of the joint, particularly arthritis (e.g. rheumatoid arthritis, osteoarthritis, 5 prosthetic joint failure), or the gastrointestinal tract (e.g. ulcerative colitis, Crohn's disease, and other inflammatory bowel diseases, gastritis and mucosal inflammation resulting from infection, the enteropathy provoked by non-steroidal antiinflammatory drugs), of the lung (e.g. adult respiratory distress syndrome, asthma, cystic fibrosis, or chronic obstructive pulmonary disease), of the heart (e.g. myocarditis), of nervous tissue (e.g. multiple sclerosis), of the pancreas (e.g. diabetes melitus and complications thereof), of the kidney (e.g. glomerulonephritis), of the skin (e.g. dermatitis, psoriasis, eczema, urticaria), of the eye (e.g. glaucoma) as well as of transplanted organs (e.g. rejection) and 10 multi-organ diseases (e.g. systemic lupus erythematosus) and inflammatory sequelae of viral or bacterial infections.

Furthermore, there is evidence for overproduction of NO by iNOS in atherosclerosis and following hypoxic or ischaemic insults (with or without reperfusion), for example in the brain or in ischaemic heart disease.

Disorders of gastrointestinal motility include ileus, for example post-operative ileus and ileus during sepsis.

By diseases of the central nervous system is meant those for which overproduction of NO is implicated, for example migraine, psychosis, anxiety, schizophrenia, sleep disorders, cerebral ischaemia, CNS trauma, epilepsy, multiple sclerosis, AIDS dementia, chronic neurodegenerative disease (e.g. 25 Lewy Body Dementia, Huntington's disease, Parkinson's disease, or Alzheimer's disease) and acute and chronic pain, and conditions in which non-adrenergic non-cholinergic nerve may be implicated such as priapism, obesity and hyperphagia.

Examples of acute pain include musculoskeletal pain, post operative 30 pain and surgical pain. Examples of chronic pain include chronic inflammatory pain (e.g. rheumatoid arthritis and osteoarthritis), neuropathic pain (e.g. post herpetic neuralgia, diabetic neuropathies associated with diabetes, trigeminal neuralgia, pain associated with functional bowel disorders, e.g. irritable bowel syndrome, non cardiac chest pain and sympathetically maintained pain) and pain associated with cancer and fibromyalgia.

Furthermore, inhibition of NO synthase may be of advantage in preventing the lymphocyte loss associated with HIV infection, in increasing the radiosensitivity of tumours during radiotherapy and in reducing tumour growth, tumour progression, angiogenesis, and metastasis.

5 Accordingly, the present invention provides a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which an inhibitor of nitric oxide synthase, for example, an iNOS inhibitor is indicated, which comprises administration of a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof. In particular, the present invention provides a method for the prophylaxis or treatment of an inflammatory and/or immune disorder, such as arthritis or asthma. In a preferred aspect the present invention provides a method for the prophylaxis or treatment of a clinical condition selected from arthritis, asthma, ileus, and migraine.

10 15 In the alternative, there is also provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for use in medical therapy, particularly, for use in the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which an inhibitor of nitric oxide synthase, for example an iNOS inhibitor, is indicated. In particular, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for the prophylaxis or treatment of an inflammatory and/or immune disorder, such as arthritis or asthma. In a preferred aspect, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for the prophylaxis or treatment of arthritis, asthma, ileus, and migraine.

20 25 30

25 The amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, and the particular disorder or disease being treated. The compounds of the invention may be administered orally or via injection at a dose of from 0.1 to 1500mg/kg per day, preferably 0.1 to 500mg/kg per day. The dose range for adult humans is generally from 5mg to 35g/day and preferably 5mg to 2g/day. Tablets or other forms of presentation provided in discrete units may conveniently contain

an amount of compound of the invention which is effective at such dosage or as a multiple of the same, for instance, units containing 5mg to 500mg, usually around 10mg to 200mg.

5 While it is possible for the compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to be administered alone, it is preferable to present it as a pharmaceutical formulation.

10 Accordingly, the present invention further provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

15 The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which an inhibitor of nitric oxide synthase, for example an iNOS inhibitor, is indicated, for example an inflammatory and/or immune disorder, such as arthritis or asthma. In a preferred aspect, there is provided a compound of formula (I), or a pharmaceutically acceptable salt, 20 solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition selected from arthritis, asthma, ileus, and migraine.

25 Hereinafter, the term "active ingredient" means a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

30 The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), inhalation (including fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers or insufflators), rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of 35 bringing the active ingredient into association with the carrier which constitutes

one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

5 Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The 10 active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert 15 diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

20 Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may 25 be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example saline or water-for-injection, immediately prior to use. Extemporaneous injection 30 solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

35 Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles

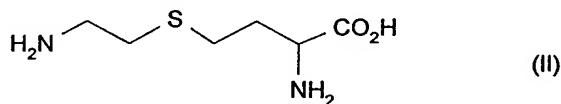
comprising the active ingredient in a basis such as gelatin and glycerin or sucrose an acacia.

Preferred unit dosage formulations are those containing an effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

According to a further aspect of the invention, there is provided a process for preparing a compound of formula (I) or a salt, solvate, or physiologically functional derivative thereof which comprises:

(i) reaction of the compound of formula (II)



or an enantiomer, a salt, or a protected derivative thereof, with a compound of formula (III)



or a salt thereof, wherein L is a leaving group, most suitably a C₁₋₆ alkoxy group, for example ethoxy, or an alkylthio, aralkylthio or arylthio group e.g. a benzylthio, or 1- or 2-naphthylmethylthio group; followed by the following steps in any order:

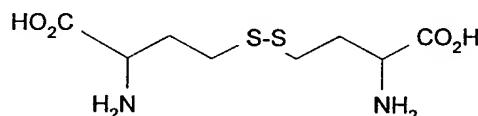
- (ii) optional removal of any protecting groups;
- (iii) optional separation of an enantiomer from a mixture of enantiomers;
- (iv) optional conversion of the product to a corresponding salt, solvate, or physiologically functional derivative thereof.

30 When L is C₁₋₆ alkoxy, the reaction in step (i) above may be effected in solution at alkaline pH, for example pH 8 to 11, suitably at pH 10.5, and at a low

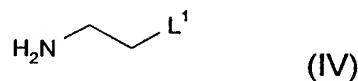
temperature, for example -5°C to 20°C, suitably 0 to 5°C. When L is an alkylthio, aralkylthio, or arylthio group, the reaction may be effected in an organic solvent e.g. tetrahydrofuran or a C₁₋₄ alcohol such as ethanol, at a moderate temperature e.g. 10 to 40°C, suitably at ambient temperature.

5 Compounds of formula (III) and salts thereof are available commercially or may be prepared by methods of organic chemistry well known to the person skilled in the art, for example, as described by Shearer *et al* in *Tetrahedron Letters*, 1997, 38, 179-182.

10 Compounds of formula (II) and salts and protected derivatives thereof may be prepared from homocystine:



15 or a protected derivative thereof, by cleaving the disulphide bond to form homocysteine or a protected derivative thereof, and coupling with a compound of formula (IV)



20 or a protected derivative thereof, wherein L¹ is a leaving group, for example halo, such as bromo, or an alkyl, aryl or aralkyl sulphonate ester, such as toluenesulphonyl.

25 Cleavage of the disulphide linkage of homocystine or a protected derivative thereof to form homocysteine or a protected derivative thereof may be effected by methods known to the person skilled in the art, for example, by use of sodium in liquid ammonia, dithiothreitol, or sodium borohydride.

30 Protected derivatives of homocysteine, eg N-t-butoxycarbonyl homocysteine t-butyl ester, may react with compounds of formula (IV) under conditions in an appropriate organic solvent (eg toluene) in a reaction mediated by a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene or a similar agent which would be recognised by one skilled in the art.

Homocystine, the compounds of formula (IV) and protected derivatives thereof are commercially available or may be prepared by methods of organic chemistry well known to the person skilled in the art.

The protecting groups used in the preparation of compounds of formula (I) may be used in a conventional manner, for example, using methods described in "Protective Groups in Organic Synthesis" by Theodora W Green, 2nd edition (John Wiley and Sons, 1991) which also describes methods for the removal of such groups.

In the above reactions, primary amines are suitably protected using acyl groups, such as t-butoxycarbonyl or benzyloxycarbonyl groups which may be removed under acidic conditions, for example, by treatment with hydrochloric acid or hydrobromic acid, or by hydrogenolysis.

As will be appreciated by the person skilled in the art use of such protecting groups may include orthogonal protection of amino groups in the compounds of formula (II) to facilitate the selective removal of one group in the presence of another, thus enabling selective functionalisation of a single amino function. For example, a benzyloxycarbonyl group may be selectively removed by hydrogenolysis. A person skilled in the art will also appreciate other orthogonal protection strategies, available by conventional means as described in Theodora W Green (*vide supra*).

The enantiomeric compounds of the invention may be obtained (a) by separation of the components of the corresponding racemic mixture, for example, by means of a chiral chromatography column, enzymic resolution methods or preparing and separating suitable diastereoisomers, or (b) by direct synthesis from the appropriate chiral intermediates by the methods described above.

Optional conversion of a compound of formula (I) to a corresponding salt may conveniently be effected by reaction with the appropriate acid or base. Optional conversion of a compound of formula (I) to a corresponding solvate or 30 physiologically functional derivative may be effected by methods known to those skilled in the art.

According to a further aspect, the present invention provides novel intermediates for the preparation of compounds of formula (I), for example: compounds of formula (II) as defined above, or an enantiomer, a salt, or a 35 protected derivative thereof; particularly, a compound selected from:

(S)-2,7-diamino-5-thioheptanoic acid;
(S)-7N-benzyloxycarbonyl-2,7-diamino-5-thioheptanoic acid;
(R,S)-2,7-diamino-5-thioheptanoic acid;
(R,S)-7N-benzyloxycarbonyl-2,7-diamino-5-thioheptanoic acid;
5 (S)-2N-t-butoxycarbonyl-2,7-diamino-5-thioheptanoic acid;
(S)-2N-t-butoxycarbonyl-7N-benzyloxycarbonyl-2,7-diamino-5-thioheptanoic acid;
(S)-t-butyl-2N-t-butoxycarbonyl-7N-benzyloxycarbonyl-2,7-diamino-5-thioheptanoate;
10 (S)-t-butyl-2N-t-butoxycarbonyl-2,7-diamino-5-thioheptanoate;
(R,S)-2N-t-butoxycarbonyl-2,7-diamino-5-thioheptanoic acid;
(R,S)-2N-t-butoxycarbonyl-7N-benzyloxycarbonyl-2,7-diamino-5-thioheptanoic acid;
15 (R,S)-t-butyl-2N-t-butoxycarbonyl-7N-benzyloxycarbonyl-2,7-diamino-5-thioheptanoate; and
(R,S)-t-butyl-2N-t-butoxycarbonyl-2,7-diamino-5-thioheptanoate.

Certain protected derivatives of the compounds of formula (I) are also useful as intermediates for the preparation of compounds of formula (I);
20 particularly a compound selected from:
(S)-2N-t-butoxycarbonyl-7N-(1-iminoethyl)-2,7-diamino-5-thioheptanoic acid;
(S)-t-Butyl-2N-t-butoxycarbonyl-7N-(1-iminoethyl)-2,7-diamino-5-thioheptanoate;
(R,S)-2N-t-butoxycarbonyl-7N-(1-iminoethyl)-2,7-diamino-5-thioheptanoic acid;
25 (R,S)-t-Butyl-2N-t-butoxycarbonyl-7N-(1-iminoethyl)-2,7-diamino-5-thioheptanoate;
and salts and solvates thereof.

For a better understanding of the invention, the following Examples are given by way of illustration.
30

SYNTHETIC EXAMPLES

EXAMPLE 1

Synthesis of (S)-[2-(1-iminoethylamino)ethyl]-L-homocysteine
35 or (S)-7N-(1-iminoethyl)-2,7-diamino-5-thioheptanoic acid

(i) (S)-7N-benzyloxycarbonyl-2,7-diamino-5-thioheptanoic acid

5 To liquid ammonia (130mL), cooled to -80°C, was added L-homocystine (3g), followed by sodium metal (1.06g) until the blue colour persisted for 15min. After this time N-benzyloxycarbonyl-ethanolamine tosylate (8.16g) was added and the reaction stirred at ambient temperature until the ammonia had evaporated. The residue was dissolved in water (80mL) and treated with 0.5M EDTA.sodium salt 10 (2mL). The pH of the solution was adjusted to 7.0 with 2N sulphuric acid and the resulting white precipitate filtered off, washed with cold water and acetone and dried in a vacuum dessicator to yield the title compound as a white solid, 5.3g.

15 Mass Spectrum M+H 313

(ii) (S)-2,7-diamino-5-thioheptanoic acid

(S)-7N-benzyloxycarbonyl-2,7-diamino-5-thioheptanoic acid (5.3g) was treated 20 with 45%HBr in acetic acid (23mL) for 1h. An intractable gum was formed and ether was added to the mixture to ensure complete precipitation of the product. The liquid was decanted off and the solids dissolved in hot SVM. This hot 25 solution was treated with pyridine until a precipitate just persisted and the mixture allowed to cool to room temperature. The resulting precipitate was filtered off and recrystallised from SVM/water to yield the title compound as a white solid, 2.2g, mp 222°C(dec).

(iii) (S)-[2-(1-iminoethylamino)ethyl]-L-homocysteine

(S)-2,7-Diamino-5-thioheptanoic acid (2.17g) was stirred in 1N NaOH (16.75mL) 30 to pH 10.5 at 0-5°C. To this solution was added ethyl acetimidate hydrochloride (2.07g) portionwise, maintaining the pH at 10.5 with 1N NaOH. When the reaction was complete the pH was adjusted to 3 with 1N HCl and the mixture applied to a Dowex AGX8 H⁺ form ion exchange column. The column was washed to neutral, then with 2.5M pyridine and again to neutral with water. 35 Elution with 0.5M ammonia and collection of the ninhydrin positive fractions,

gave after evaporation. The resulting residue was treated with 1N HCl to pH 4.5, evaporated to dryness. The residue was then treated with ethanol and evaporated to dryness and then with diethyl ether and diethyl ether and evaporated to dryness to give the monohydrochloride of the title compound as a

5 hard white foam.

The microanalysis of the product was consistent with the 1.75 hydrate:
found (calculated): C 33.56 (33.45); H 7.11 (7.49), N 13.74 (14.63)

10 EXAMPLE 2

(R/S)-[2-(1-iminoethylamino)ethyl]-D,L-homocysteine was prepared by methods analogous to those used in Example 1, starting from D,L-homocystine.

15 The ¹H NMR of the product was consistent with the proposed structure.

EXAMPLE 2a

20 The racemic product of Example 2 was substantially resolved into the two constituent enantiomers [identical to the (S) product in Examples 1 and 4 and the (R) product in Example 3] using a chiral Crownpac (+) HPLC column and elution with aqueous trifluoroacetic acid at pH2.

(S)-[2-(1-iminoethylamino)ethyl]-L-homocysteine

25 The microanalysis of the product was consistent with the ditrifluoroacetate salt hydrate C₈H₁₇N₃O₂S.(CF₃CO₂H)₂.H₂O
found (calculated): C 31.06 (30.97); H 4.53 (4.55), N 9.08 (9.03)
CD spectrum (0.1N aq HCl) 210 (+0.80) nm.

30 (R)-[2-(1-iminoethylamino)ethyl]-D-homocysteine

The microanalysis of the product was consistent with the salt form .1.67 trifluoroacetate .0.3 HCl .1.5hydrate C₈H₁₇N₃O₂S.(CF₃CO₂H)_{1.67}.HCl_{0.3}.1.5H₂O
found (calculated): C 30.18 (30.40); H 4.92 (4.97), N 9.53 (9.41), S 7.41 (7.18), Cl 1.86 (2.38), F 21.36 (21.28).

35 CD Spectrum (0.1N aq HCl) 210 (-0.64) nm.

EXAMPLE 3

(R)-[2-(1-iminoethylamino)ethyl]-D-homocysteine was prepared by methods analogous to those used in Example 1, starting from D-homocystine.

EXAMPLE 4Synthesis of (S)-[2-(1-iminoethylamino)ethyl]-L-homocysteine

To liquid ammonia (430mL) cooled to -80°C, was added L-homocystine (10g, 37.45mmol). The cooling bath was removed and sodium metal (3.18g, 138.26mmol) was added portionwise over 25min allowing the temperature to

rise to reflux temperature. Stirring was continued at reflux for a further 30min, after which time N-benzyloxycarbonyl-ethanolamine tosylate (25g, 74.9mmol) was added and the reaction stirred at ambient temperature overnight until the ammonia had evaporated. The residue was stirred with water (250mL) at 40°C for 10min, cooled to room temperature and filtered. The pH of the solution was adjusted to 7.0 with 2M sulphuric acid and the resulting white precipitate filtered off, washed with cold water and acetone and dried in a vacuum dessicator to yield (S)-7N-benzyloxycarbonyl-2,7-diamino-5-thioheptanoic acid as a white solid, Mp 240°C(dec).

(ii) (S)-2N-t-butoxycarbonyl-7N-benzyloxycarbonyl-2,7-diamino-5-thioheptanoic acid

(S)-7N-benzyloxycarbonyl-2,7-diamino-5-thioheptanoic acid (15.5g, 49.67mmol) was added to sodium hydroxide (6.357g, 159mmol) in water (110mL) followed by dioxane (55mL). To this mixture was added di-t-butylidicarbonate (16.26g, 74.5mmol) and the mixture stirred overnight at room temperature under nitrogen. After this time the precipitated solids were filtered off, toluene (300mL) added, and the layers separated. The aqueous layer was cooled and made acidic to pH ~3 using 1N HCl. The acidified fraction was extracted with toluene (4x100mL) and ethyl acetate (3x100mL), and the combined organic fractions

dried over MgSO_4 . Concentration of the combined organics under reduced pressure to give (S)-2N-t-butoxycarbonyl-7N-benzyloxycarbonyl-2,7-diamino-5-thioheptanoic acid as a white gum.

Mmass spectrum M+H 413

5

(iii) (S)-2N-t-butoxycarbonyl-2,7-diamino-5-thioheptanoic acid formate salt

To methanol (50mL) cooled to 5°C under a nitrogen atmosphere was added palladium black (0.678g) all at once. To this cooled solution was added a mixture of methanol (50mL) and formic acid (11mL, 196mmol) over 1min followed by the addition of (S)-2N-t-butoxycarbonyl-7N-benzyloxycarbonyl-2,7-diamino-5-thioheptanoic acid (2g, 4.85mmol) in methanol (50mL) over 2min. The mixture was allowed to stir overnight at ambient temperature, more palladium black (257mg) added and stirring continued for a further 3h. The reaction mixture was filtered through Hyflo and concentrated under reduced pressure. The residue was partitioned between water and ethyl acetate, the aqueous layer washed with more ethyl acetate, and the aqueous layer concentrated to yield (S)-2N-t-butoxycarbonyl-2,7-diamino-5-thioheptanoic acid formate salt as a white solid.

15

Mass Spectrum M+H 279 (65%), 223 (100%)

(iv) (S)-2N-t-butoxycarbonyl-7N-(1-iminoethyl)-2,7-diamino-5-thioheptanoic acid hydrochloride

To (S)-2N-t-butoxycarbonyl-2,7-diamino-5-thioheptanoic acid formate salt (2.154g, 6.59mmol) in ethanol (50mL) at room temperature under nitrogen was added S-(1-naphthylmethyl)thioacetimidate hydrochloride (3.70g, 14.75mmol) followed by ethanol (50mL). Stirring at ambient temperature, the solids dissolved after 2h and the solution stirred overnight. The reaction was concentrated *in vacuo*, the residue treated with water, and the aqueous fraction washed with diethyl ether (4x50mL). Concentration of the aqueous fraction *in vacuo* gave (S)-2N-t-butoxycarbonyl-7N-(1-iminoethyl)-2,7-diamino-5-thioheptanoic acid hydrochloride as a white hygroscopic solid.

Mass spectrum M+H 320 (75%), 264 (100%), 220 (15%)

(v) (S)-[2-(1-iminoethylamino)ethyl]-L-homocysteine

To (S)-2N-t-butoxycarbonyl-7N-(1-iminoethyl)-2,7-diamino-5-thioheptanoic acid hydrochloride (3.086g, 8.69mmol) was added slowly 4N HCl/dioxane (20mL)

5 and the reaction mixture stirred at ambient temperature overnight. The reaction was concentrated *in vacuo*, the residue dissolved in water and washed with diethyl ether (3x20mL). The aqueous layer was concentrated *in vacuo* to yield the title compound as the hydrochloride, as a hygroscopic solid.

Mass Spectrum M+H 220;

10 ^1H NMR(D₂O) δ : 2.1-2.35 (5H,m), 2.76 (2H,t), 2.87 (2H,t), 3.51 (2H,t), 4.12 (1H,t).

EXAMPLE 515 Synthesis of (S)-[2-(1-iminoethylamino)ethyl]-L-homocysteine(i) (S)-t-butyl-2N-t-butoxycarbonyl-7N-benzyloxycarbonyl-2,7-diamino-5-thioheptanoate

20 To a solution of N-t-butoxycarbonyl cysteine t-butyl ester (prepared by reduction of N-t-butoxycarbonyl cystine t-butyl ester with dithiothreitol) (291 mg, 1 mmol) in dry toluene (20 ml) is added N-benzyloxycarbonyl ethanolamine tosylate (349 mg, 1 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (150 μL , 1 mmol) and the mixture stirred vigorously overnight at room temperature under nitrogen. The
25 mixture is partitioned between 50 ml each of ethyl acetate and 1N aqueous HCl. A further organic extract is combined and these extracts washed with aqueous sodium bicarbonate, water and brine, then dried and evaporated. Purification by column chromatography affords the title compound.

Mass Spectrum M+H 469 (25%), 369 (100%)

30 In an alternative method, conversion of the product from Example 4, step (ii) to its t-butyl ester using either N,N-dimethylformamide di-O-t-butyl acetal or O-t-butyl 1,1,1 trichloroacetimidate gave the title compound as a white crystalline solid.

(ii) (S)-t-butyl-2N-t-butoxycarbonyl-2,7-diamino-5-thioheptanoate formate salt

To a solution of (S)-t-butyl-2N-t-butoxycarbonyl-7N-benzyloxycarbonyl-2,7-diamino-5-thioheptanoate (1 g, 2.1 mmol) in ethanol (50 ml) was added 5 palladium hydroxide on carbon (20%, 0.5 g) and ammonium formate (1.34 g). The suspension was refluxed for 2.5 h, cooled and filtered through a plug of silica which was well washed with 1:1 ethanol-water and evaporated to afford the title compound as a formate salt.

Mass Spectrum M+H 335

10

(iii) (S)-t-Butyl-2N-t-butoxycarbonyl-7N-(1-iminoethyl)-2,7-diamino-5-thioheptanoate hydrochloride

15 The crude (S)-t-butyl-2N-t-butoxycarbonyl-2,7-diamino-5-thioheptanoate formate salt from step (ii) was slurried with 50 ml of tetrahydrofuran, the liquid decanted and mixed with S-(1-naphthylmethyl)thioacetimidate hydrochloride (0.5 g, 2 mmol) and stirred for 24 hours at room temperature. The solvent was evaporated and the residue partitioned between 25 ml each of ether and water, followed by 2 ether washes; back aqueous extracts were combined and 20 evaporated to give a white paste. This was freeze dried twice to afford the title compound as a white hygroscopic solid.

Mass spectrum M+H 376 (100%), 320 (15%), 276 (12%).

(iv) (S)-S-[2-(1-iminoethylamino)ethyl]-L-homocysteine

25 Deprotection of (S)-t-Butyl-2N-t-butoxycarbonyl-7N-(1-iminoethyl)-2,7-diamino-5-thioheptanoate hydrochloride using 4N HCl in dioxane, by methods analogous to those used in Example 4 step (v), afforded (S)-S-[2-(1-iminoethylamino)ethyl]-L-homocysteine.

30 The characterising data for the title compound was consistent with that for the product of Example 4.

BIOLOGICAL ACTIVITY1. Inhibition of eNOS and iNOS in rat aortic rings

5 The inhibition of eNOS and iNOS *in situ* in rat aortic rings was assessed by measuring the increases in ring tension caused by NO synthase inhibition. For studies of basal tone (reflecting eNOS), rings of thoracic aorta with intact endothelium were prepared as described previously (Rees *et al.* (1989) Br. J. Pharmol. 96, 418-424) and cumulative concentration curves obtained for the 10 inhibitors in the presence of a threshold concentration of phenylephrine ($ED_{10} \approx 10\text{nM}$). For studies of induced smooth muscle tone (reflecting iNOS), endothelium-denuded rings were exposed to LPS (0.1 $\mu\text{g}/\text{ml}$ from *S.typhosa*) in the presence of phenylephrine at approximately ED_{90} for 6h as described previously (Rees *et al.* (1990) Biochem. Biophys. Res. Commun. 173, 541- 15 547). During this time a progressive loss of tone occurred because of iNOS induction. Cumulative concentration curves were then obtained for the 20 inhibitors.

The results are given in the following table:

20

	iNOS $IC_{50}(\mu\text{M})$	eNOS %inhib@300 μM	selectivity iNOS vs eNOS
Example 1	0.73	43	>500 fold
Example 2	0.45	53	>500 fold
Example 3	6.6	20	>150 fold

25

By contrast, 2-(1-iminoethylamino)ethyl cysteine hydrochloride (Example 4 of WO93/13055) is only 33 fold selective for iNOS versus eNOS in the same test.

2. Inhibition of nNOS in rat cortical slices

30

The effects of compounds on nNOS in rat brain slices was determined as described in Furfine *et al* (1994) J. Biol. Chem. 269, 26677-26683 and Lizasoain *et al* (1995) J. Neurochem. 64, 636-642.

5 KCl (54mM) - stimulated NO synthesis was measured by the conversion of 14C-arginine to 14C-citrulline over a 2h period at 37°C in McIlwain - chopped (0.2mm x 0.2mm) rat cerebral cortex slices, following a 1h preincubation period in the absence of compound or high KCl.

The compound of Example 1 was determined to have an IC₅₀ of 220µM, suggesting approximately 300-fold selectivity for iNOS versus nNOS.

10 3. Method for determining the oral bioavailability of iNOS inhibitor compounds

Animal work:

15 Mice (3 animals per time point) were dosed intravenously (10 mg/kg) and orally (50 mg/kg) with test compound in an aqueous solution. Blood samples were taken at time intervals after administration and plasma prepared by centrifugation. Samples were stored at -20°C until analysis.

20 Analysis of compounds in plasma:

25 Plasma (50µl) was de-proteinated and compound derivatised with a quaternary ammonium reagent. Samples were then injected onto an HPLC system and compound concentration determined using mass spectrometric detection.

25 Pharmacokinetic analysis:

30 The plasma concentrations obtained by the above method were entered into a pharmacokinetic software package (PKCAL v 1.2s) and the data were fitted using a non-compartmental method. The oral bioavailability of the compounds was determined by comparing the Area Under the Curve (AUC) values calculated by the software for the oral profile with the AUC for the intravenous profile. The half-lives were obtained by fitting the terminal phase time points of the intravenous profile.

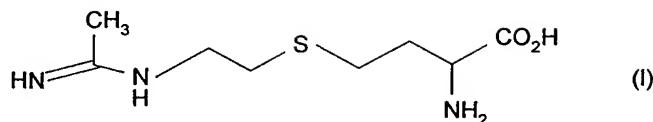
(S)-[2-(1-iminoethylamino)ethyl]-L-homocysteine was found to have an oral bioavailability of 55% and a half-life of 5.7h.

When repeated at iv and oral doses of 10mg/kg in rats, (S)-[2-(1-

5 iminoethylamino)ethyl]-L-homocysteine had a bioavailability of 92%.

Claims

1. A compound of formula (I);



or a salt, solvate, or physiologically functional derivative thereof.

10 2. A compound of formula (I) selected from:

(R/S)-[2-(1-iminoethylamino)ethyl]-DL-homocysteine

(S)-[2-(1-iminoethylamino)ethyl]-L-homocysteine; and

(R)-[2-(1-iminoethylamino)ethyl]-D-homocysteine

15 or a salt, solvate, or physiologically functional derivative thereof.

10 3. The compound of formula (I) which is (S)-[2-(1-iminoethylamino)ethyl]-L-homocysteine or a salt, solvate or physiologically functional derivative thereof.

20 4. A method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which an inhibitor of nitric oxide synthase is indicated, which comprises administration of a therapeutically effective amount of a compound of formula (I) as defined in any of claims 1 to 3, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

25 5. A method according to claim 4 wherein the clinical condition is selected from arthritis, asthma, ileus, and migraine.

30 6. A compound of formula (I) as defined in any of claims 1 to 3 or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for use in medical therapy.

7. A pharmaceutical formulation comprising a compound of formula (I) as defined in any of claims 1 to 3 or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

5

8. Use of a compound of formula (I) as defined in any of claims 1 to 3 or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which an inhibitor of nitric oxide synthase is indicated.

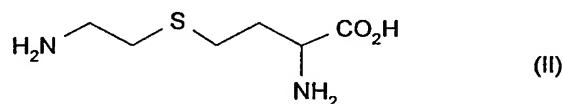
10

9. Use according to claim 8 wherein the clinical condition is selected from arthritis, asthma, ileus, and migraine.

15

10. A process for preparing a compound of formula (I) or a salt, solvate, or physiologically functional derivative thereof which comprises:

(i) reaction of the compound of formula (II)



20

or an enantiomer, a salt, or a protected derivative thereof, with a compound of formula (III)



25

or a salt thereof, wherein L is a leaving group; followed by the following steps in any order:

- (ii) optional removal of any protecting groups;
- (iii) optional separation of an enantiomer from a mixture of enantiomers;
- (iv) optional conversion of the product to a corresponding salt, solvate, or physiologically functional derivative thereof.

30

11. A compound selected from:

(S)-2,7-diamino-5-thioheptanoic acid;

(S)-7N-benzyloxycarbonyl-2,7-diamino-5-thioheptanoic acid;

(R,S)-2,7-diamino-5-thioheptanoic acid;

5 (R,S)-7N-benzyloxycarbonyl-2,7-diamino-5-thioheptanoic acid;

(S)-2N-t-butoxycarbonyl-2,7-diamino-5-thioheptanoic acid;

(S)-2N-t-butoxycarbonyl-7N-benzyloxycarbonyl-2,7-diamino-5-thioheptanoic acid;

(S)-t-butyl-2N-t-butoxycarbonyl-7N-benzyloxycarbonyl-2,7-diamino-5-

10 thioheptanoate;

(S)-t-butyl-2N-t-butoxycarbonyl-2,7-diamino-5-thioheptanoate;

(R,S)-2N-t-butoxycarbonyl-2,7-diamino-5-thioheptanoic acid;

(R,S)-2N-t-butoxycarbonyl-7N-benzyloxycarbonyl-2,7-diamino-5-thioheptanoic acid;

15 (R,S)-t-butyl-2N-t-butoxycarbonyl-7N-benzyloxycarbonyl-2,7-diamino-5-thioheptanoate; and

(R,S)-t-butyl-2N-t-butoxycarbonyl-2,7-diamino-5-thioheptanoate.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/00096

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C323/58 A61K31/195 C07C323/59

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	FR 2 727 111 A (LABORATOIRES HOECHST) 24 May 1996 see example 11	11
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X	EP 0 068 173 A (MERCK & CO) 5 January 1983 see examples 14,15 ----	11 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

Int. Appl. No.
PCT/EP 98/00096

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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